JUL 21 2004

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	15.Jul.04	MAJOR REPORT

4. TITLE AND SUBTITLE
CONTINUED USE OF ZONISAMIDE FOLLOWING DEVELOPMENT OF RENAL CALCULI

5. FUNDING NUMBERS

6. AUTHOR(S)
MAJ RICHARDS KAREN C

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
BAYLOR COLLEGE OF MEDICINE

8. PERFORMING ORGANIZATION REPORT NUMBER
CI04-438

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
THE DEPARTMENT OF THE AIR FORCE
AFIT/CIA, BLDG 125
2950 P STREET
WPAFB OH 45433

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT
Unlimited distribution
In Accordance With AFI 35-205/AFIT Sup 1

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

DISTRIBUTION STATEMENT A
Approved for Public Release
Distribution Unlimited

20040730 029

14. SUBJECT TERMS	15. NUMBER OF PAGES
	7
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

CONTINUED USE OF ZONISAMIDE FOLLOWING DEVELOPMENT OF RENAL CALCULI

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(Disclosure: Consulting - Elan Pharmaceuticals, Honoraria - Elan Pharmaceuticals)

The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government.

The reported incidence of renal calculi complicating Zonisamide (ZNS) therapy for epilepsy ranges from 0.2 to 4.4%.[1-3] Typically this complication leads to discontinuation of the drug. For patients uniquely responsive to Zonisamide, the benefits of continued treatment may outweigh the risk of calculus recurrence. We report three patients who developed nephrolithiasis but continued ZNS treatment without recurrence of calculi.

Case 1:

A 43 year old man with symptomatic generalized epilepsy, mental retardation and cerebral palsy since infancy initiated ZNS 900 mg/day, added to previous therapy with valproate and diazepam. His seizures decreased from 4-5 per week to rare events. One year later he developed flank pain, dysuria, and gross hematuria. An abdominal CT showed multiple calculi in the left kidney and ureter. His pain resolved with hydration, but discontinuation of ZNS led to recurrence of frequent seizures. ZNS was restarted after alternative anticonvulsants failed. He initiated calcitrate to decrease risk of stone recurrence. Two renal ultrasounds 3 and 29 months later demonstrated no renal calculi. Forty-five months later he averages one seizure per month on ZNS 400 mg/day with no symptoms of calculi.

Case 2:

Seizures in a 20 year old with localization-related epilepsy decreased by over 50% when ZNS 400 mg/day was added to levitiracetam and oxcarbazepine. He developed flank pain 10 months after starting ZNS, and a renal ultrasound confirmed a calculus in the ureter. His pain resolved with hydration and the stone passed. He elected to continue

treatment with ZNS due to marked reduction in seizures. A renal ultrasound 4 months later demonstrated no renal calculi. He remained free of symptoms of recurrence of calculi 29 months later, when escalation of seizures led to transition from ZNS to topiramate.

Case 3:

A 28 year old with supplementary motor area seizures, a family history of nephrolithiasis, and a personal history of nephrolithiasis during topiramate therapy developed pain and hematuria after 18 months on ZNS 600 mg/day. Renal ultrasound confirmed the presence of a calculus, which he then excreted spontaneously. Due to a greater than 90% reduction in seizure frequency since initiation of ZNS, he elected to continue treatment with ZNS and increased oral hydration. He has had no recurrence of symptoms of calculi 42 months later.

The development of renal calculi during ZNS treatment led to the temporary suspension of clinical trials in the USA.[1] Calculi may develop more commonly in nonambulatory patients, as in our first case, and in patients with a family history of nephrolithiasis, as our third case.[1,2] Two other anticonvulsants, acetazolamide (AZA) and topiramate (TPM) have also been linked to nephrolithiasis. AZA, TPM and ZNG all inhibit carbonic anhydrase, although the inhibitory potency of ZNS is 100 fold less than that of AZA.[1] Nephrolithiasis during acetazolamide therapy has been attributed to alkalinization of the urine, increased calcium excretion, and decreased urinary citrate, which inhibits calcium phosphate crystallization. [3-5]

There is precedence for continuing treatments associated with nephrolithiasis in patients who develop renal stones. A prospective study of 10 patients who continued acetazolamide after developing renal stones showed that 5 (50%) experienced a recurrence within a median of 10 months.[5] Additionally, Kossoff et al reported continuing the ketogenic diet (also known to promote nephrolithiasis) in patients despite development of renal calculi.

Strategies for management of patients who developed calculi and continue the suspected causative agent have not been studied. Some authors suggest monitoring urine output, or screening regularly for hematuria while others promote annual screening KUBs or renal ultrasounds, with pre-emptive litotripsy when asymptomatic stones are discovered.[1,3,6] Since the recurrence rate of renal calculi during continued ZNS treatment is unknown, the yield and cost-effectiveness of these surveillance tests cannot be assessed. Increased fluid intake has proven efficacy in preventing recurrence of nephrolithiasis from any cause, decreasing recurrence by 50% in one study.[7] Citrate supplementation is another rational strategy, given the hypocitraturia documented in acetazolamide treatment, but hydration alone may be adequate. Dietary calcium should not be restricted, as this may promote bone loss.[7] Consultation with a nephrologist may identify other modifiable patient-specific factors that could affect recurrence risk, such as hypercalciuria.

These cases illustrate that some patients who develop nephrolithiasis during ZNS treatment may tolerate continued long-term use of ZNS without recurrence. In patients with distinctive responsiveness to ZNS, the development of renal calculi need not be an absolute indication to discontinue treatment. Daily fluid intake should be increased to decrease risk of recurrence.

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Title character count: 66

Word count: 729